

**UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
SAN FRANCISCO, CALIFORNIA 94143-0444**

August 13, 1996

Carol L. Francis, Ph.D.
Patent Agent
Fish and Richardson, P.C.
2200 Sand Hill Road
Menlo Park, California 94025
[Fax: 415-854-0875]

Dear Carol:

Thank you for the new draft of our patent application (96-106-1). Here are my comments and corrections. They are minor. I hope you received the new graph and description of the experiment that I sent you.

2.25 "by a non-invasive procedures." delete "a"

3.29 "complex factory procedure transformed cells" to "to transform cells"

6.18 Figure descriptions. I believe the construct at the bottom of figure 1 was used in the experiment with insulin that I just sent you. Please check it out with Mike German. In any event, the construct that was used should be included.

10.5 Citations for intestinal, cell specific promoters. Ask Mike German

12.4 "eukaryotic promoter" Is term properly used for CMV RSV, etc.?

14.27 "the normal blood" delete "normal"

18.13 "which" to "that"

20. table 2 Intrinsic factor deficiency is listed under "autoimmune diseases" It is also listed under Gastrointestinal and pancreatic deficiencies, where I think it belongs. What happened to examples of autoimmune diseases. Ask Ira and Mike for examples. Also, does footnote #2 refer to APO A1? If so, it is given as a subscript.

21.24 "disrupted." delete period

22.23 "secretion into these cells" to "secretion of these cells"

23.18 VIP - vasoactive intestinal peptide; GIP - gastric inhibitory peptide. Ask Mike German and Ira Goldfine for others.

24.2 "systems" to "system"

27.26 "expression in the mammalian"

32.29 delete "the presence of the protein in"

35.9 "pentabarbital" ? Please check spelling of this word wherever used.

35.14 "A 5 cm with 128 μ g of dendrimers." insert after "lumen of the bowel."

35.31 Delete "The solution side effects."

36.8 Response from Mike German

36.14,15 delete

37.6 I sent you description of experiment to be added to this list. Drs. German and Goldfine can fill in description here of the various prototypical experiments.

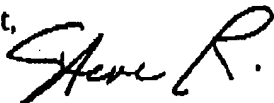
40.12 "Further claims to be included" I think Mike German can add this material.

43.3 "Describe how therapeutic protein expressions and/or secretion can be enhanced by hormonal stimulation." For secretion, not too much is known, other than cholinergic stimulation enhances secretion from intestinal glands, and so does CCK. Maybe Mike or Ira know more. Also, regarding expression, the only thing that I can think of is the augmented expression of brush border enzymes such as sucrase and lactase by increasing the ingestion of the relevant foodstuff.

43.15 "Is above correct?" Probably, but partitioning of product secreted from intestinal cells has not been studied to my knowledge, except that CCK is released both into the gut and blood from intestinal endocrine cells. Mike and Ira?

I hope this gets us close to the finished product. Thanks for your help and good work! Since I am away, I wonder if I could impose on you to fax my comments to Ira and Mike.

My best,



Stephen Rothman
Professor

FISH & RICHARDSON P.C.

FISH RICHARDSON & NEAVE
BOSTON
(617-542-8070)

FREDERICK P. FISH
(1935-1990)

W.M. RICHARDSON
(1959-1991)

2200 SAND HILL ROAD, SUITE 100
MENLO PARK, CALIFORNIA 94025

TELEPHONE: 415/322-5070
FAX: 415/854-0878

BOSTON
617/542-8070
WASHINGTON, D.C.
202/785-8070

HOUSTON
713/625-8070

TWIN CITIES
612/335-8070

SOUTHERN CALIFORNIA
619/678-8070

NEW YORK
212/785-8070

August 13, 1996

Our File: 06510/048001

BY FACSIMILE
(415) 731-3612

Dr. Michael German
Hormone Research Institute
1090 HSW, Box 0534
University of California
San Francisco, CA 94143

Dr. Rothman's Comments for
Draft of U.S. Patent Application
for SYSTEMIC GENE THERAPY BY INTESTINAL CELL EXPRESSION
Inventor(s): German et al.
U.C. Case No.: 96-106-1
Our Ref.: 06510/048001

Dear Dr. German:

Further to my letter of August 8, 1996 enclosing the revised draft patent application for the above-referenced invention, please find enclosed a copy of a letter received today from Dr. Rothman detailing his comments on the draft. In addition to his letter dated August 13, I have also received a letter from Dr. Rothman dated August 8, enclosing the experimental diabetes data.

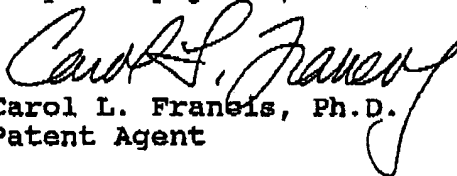
I plan to revise the draft application according to Dr. Rothman's comments within the next week. If you have any additional comments that I may include with Dr. Rothman's revisions, please forward them to me at your earliest convenience.

FISH & RICHARDSON P.C.

Dr. Michael German
August 13, 1996
Page 2

I look forward to hearing from you. If you have any questions, I can be reached at (415) 233-2115.

Very truly yours,


Carol L. Francis, Ph.D.
Patent Agent

CLF/dst

Enclosures

cc: Dr. Ira D. Goldfine (w/encl. by facsimile)

46993.P11